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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/630,846	08/02/00	THOMPSON J	030206.0179.

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EXAMINER	
LACOURCIERE, K	
ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 11/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/630,846	THOMPSON, JAMES D.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(1). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-17 and 20-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 6,146,886. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claims encompass RNA molecules which overlap in scope with the RNA molecules encompassed by the patented claims. For example, it appears that the instantly claimed

therapeutic RNA molecules, which have a desired RNA portion and a region of 3' and 5' complementarity, would encompass the patented RNA molecules, which are limited to molecules wherein the desired RNA portion (which encompasses therapeutic RNA) must fall between the region of 3' and 5' complementarity.

Claims 1-17 and 20-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 5,902,880. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claims encompass RNA molecules which overlap in scope with the RNA molecules encompassed by the patented claims. For example, the instantly claimed RNA molecules would encompass the RNA molecules with the patented structures, including RNA molecules with the polymerase III A box and B box and a desired RNA (which would include a therapeutic RNA) either 5', 3' or between said A and B box.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-9, 12, 13, 15-19, 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-9 and 24 recite the limitation "said desired RNA molecule". There is insufficient antecedent basis for this limitation in the claim. Claims 6-9 and 24 are further indefinite because the metes and bounds of the term "desired RNA molecule" are unclear, for example, as to what characteristics of an RNA molecule would render one RNA molecule desired over another RNA molecule. The scope of the claimed RNA molecules is unclear. Claim 25 is indefinite for the same reasons due to its dependence on claim 24.

Claims 12, 13 and 15-19 are indefinite because of the absence of an article in the preamble of the claims, rendering the scope of the preamble indefinite. This claim appears to follow the European style, whereas in U.S. practice independent claims normally contain an article in the preamble.

Claim 19 recites the limitation "The method" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 19 recites the limitation "said introducing" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 19 is indefinite because it recites a method, however it depends on a composition claim, and is unclear what method is being claimed.

For the purposes of the examination of the instant case, claim 19 is being considered as being a method, wherein the method provides further limitations to the method of claim 18.

Claim 18 is indefinite because the metes and bounds of the term "desired RNA molecule" are unclear, for example, as to what characteristics of an RNA molecule would render one RNA molecule desired over another RNA molecule. The scope of the RNA molecule of the claimed method is unclear.

Claim 18 is further indefinite because the language of the claim is confusing, specifically, it is unclear whether the method comprises the step of introducing said molecule into the cell or introducing an RNA comprising a desired RNA molecule into said cell. Also, it is unclear if the phrase "having a 5' terminus able to pair with at least 8 bases of a 3' region of said RNA molecule" is meant to modify the "desired RNA molecule" or "a RNA comprising a desired RNA molecule".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of introducing an RNA molecule into a cell in vitro (cell culture), does not reasonably provide enablement for a method of introducing an RNA molecule into a cell in vivo (whole organism) nor does the specification reasonably provide enablement for

a transcribed RNA molecule which comprises a therapeutic portion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-17 and 20-25 are drawn to a transcribed RNA molecule wherein the RNA comprises a therapeutic portion. Claims 18 and 19 are drawn to a method of providing a desired RNA molecule to a cell, wherein the RNA molecule is transcribed, including from a vector. These claims encompass methods of introducing an RNA molecule into a cell in vitro (cell culture) or in vivo (whole organism).

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The specification has provided examples wherein Applicant has demonstrated transfer of an RNA molecule to a cell in vitro(cell culture), however, the specification clearly indicates that the claimed methods would encompass the transfer of an RNA molecule to a cell in vivo (whole organism) for therapeutic purposes (ie. gene therapy). The specification does not provide any examples wherein an RNA molecule is provided to a cell in vivo(whole organism). Further, these claims are drawn to transcribed RNA molecules wherein the RNA molecule comprises a

therapeutic portion, however, the specification has not provided any examples of RNA molecules which have therapeutic properties.

At the time the instant invention was made, and even to date, gene therapy methods are highly unpredictable, particularly with regard to the delivery of an RNA molecule or vector to a cell and expression from said vector (see for example Orkin et al., Anderson, Verma et al.) and in vitro methods typically do not translate into success in vivo. Further, even if a molecule can be successfully delivered into a cell, to result in a therapeutic effect the expression of the oligonucleotide must be sufficient to provide the therapeutic effect or block the expression of a gene. The level of expression required varies dependent upon the disease state which is treated. Expression of vectors *in vivo*(whole organism) is unpredictable, often too low for therapeutic effects or unexpectedly turned off (see Verma et al., for example). Effective expression requires an appropriate promoter-enhancer combination, "the search for such combinations is a case of trial and error for a given type of cell"(see Verma, for example, p 240). Applicant has not provided any guidance as to how to deliver their oligonucleotide to a specific target cell in vivo or whether their promoter would result in sufficient expression in any target cell to provide a therapeutic effect. The amount of experimentation to make an use the claimed method to provide an RNA to a cell in vivo (whole organism), or provide a therapeutically effective RNA is very high. Due to the lack of specific guidance, one skilled in the art would need to practice undue trial and error experimentation to practice the methods of delivery, as claimed, over the full scope claimed. This experimentation would require the determination of how to specifically deliver the

claimed RNA molecule, or a vector expressing such, to a target cell in vivo (whole organism), or provide said RNA as a therapeutic molecule.

Therefore, due to the broad breadth of the claims, the nature of the invention, the high unpredictability of the art, the lack of sufficient guidance provided by the inventor, the lack of working examples, and the quantity of experimentation required, it would have required undue trial and error experimentation for one skilled in the art to practice the invention as claimed, over the full scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 9-12, 15-19, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Inouye (US Patent No. 5,208,149).

Inouye discloses a non-naturally occurring RNA molecule which comprises an intermolecular stem structure of more than 8 bases and wherein the RNA comprises an antisense molecule, wherein the RNA is encoded by a vector and in a cell and wherein the RNA is separated

from the intramolecular stem by a spacer region. Inouye disclose their RNA as comprising a therapeutic portion (e.g. to block the expression of harmful genes, such as oncogenes and viral genes). Therefore, Inouye anticipates claims 1, 9-12, 15-19, 24 and 25.

Claims 1, 2, 9-19, 21, 24 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Noonberg et al. (US Patent No. 5,624,803).

Noonberg et al. disclose RNA polymerase based constructs for generating oligonucleotides wherein the construct comprises a U6 RNA polymerase III promoter, and a region comprising a desired RNA, including a therapeutic RNA (for example, antiviral or anticancer) and wherein the RNA comprises a region of complementarity between a 5' region and a 3' region (intramolecular stem region) which is generally between about 8 and about 30 nucleotides in length (see for example col 15, lines 45-50). The RNA disclosed by Noonberg et al. includes an RNA which comprises an antisense oligonucleotide, a ribozyme, a triplex-forming molecule or combination (see for example col 14, lines 60-64). The RNA disclosed by Noonberg et al. is transfected into cells (see for example col 23, lines 35-67). Therefore, Noonberg et al. anticipates claims 1, 2, 9-19, 21, 24 and 25.

Conclusion

Any inquiry concerning this communication should be directed to Karen A. Lacourciere at telephone number (703) 308-7523. The Examiner can normally be reached from 8:30 am to 6:30 pm Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
October 31, 2001

SEAN McGARRY
PRIMARY EXAMINER